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Multisystemic inflammatory syndrome in children associated with COVID-19: a single center experience in Turkey

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What is already known on this topic?

- *Multisystem inflammatory syndrome in children (MIS-C) associated with the coronavirus disease 2019 (COVID-19) is a new concern emerging as a severe presentation of COVID-19 in children.*
- *Myocardial and gastrointestinal involvement were more prominent in patients with MIS-C.*
- *Laboratory findings, such as lymphopenia and thrombocytopenia, are common, which were unexpected in Kawasaki disease.*

What this study adds on this topic?

- *This study involves a series of children with MIS-C showing favorable clinical outcomes in Turkey.*
- *Cardiac manifestations are common, including ventricular dysfunction and coronary artery dilatation. Hence, all patients should be evaluated for cardiac involvement.*
- *Our center is situated in an industrial region where the population is younger and cities have more children as a percentage of the population. Therefore, our study is important to characterize the clustered cases of MIS-C.*

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ABSTRACT

Objective: Multisystem inflammatory syndrome in children (MIS-C) associated with the coronavirus disease 2019 (COVID-19) is a new concern emerging as a severe presentation of COVID-19 in children. We aimed to describe the characteristics and short-term outcomes of children diagnosed with MIS-C.

Material and Methods: A retrospective study was conducted on 24 patients who were diagnosed with MIS-C between June 1, 2020 and December 1, 2020. A total of 24 (14 male and 10 female) patients were included in the study.

Results: The median age at the diagnosis was 111 (10-180) months. A total of 17 patients had a history of contact with a patient with COVID-19. Among the 24 patients, the most common findings were gastrointestinal involvement (n=20), followed by conjunctivitis (n=12), erythematous rash (n=11), and oral changes (n=10). Cardiovascular involvement was detected in 12 patients, of whom six had systolic dysfunction, four had mild coronary artery involvement, four had pericardial effusion, and three had mitral insufficiency. All patients received intravenous immunoglobulin, and 14 patients were treated with methylprednisolone in addition. Anti-interleukin-1 was given to two patients. The median duration of hospitalization was 8 (5-15) days. A total of 23 patients were discharged and evaluated on the median of 68.5 (52-140) days after discharge. The remaining one patient with dilated cardiomyopathy died after 2 months in the intensive care unit.

Conclusion: Increasing the knowledge on MIS-C will provide clinicians with information on early recognition, evaluation, and management of these patients.

Keywords: COVID-19, Kawasaki disease, MIS-C, MIS-C associated with COVID-19

Introduction

Coronaviruses are a group of RNA viruses belonging to the Orthocoronavirinae subfamily of the Coronaviridae family capable of causing infections in both humans and animals. In December 2019, a cluster of atypical viral pneumonia cases with similar characteristics emerged in Wuhan, Hubei province, China (1). A new type of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was announced as a causative viral agent, and the new disorder was officially named coronavirus disease 2019 (COVID-19) on February 11, 2020. Subsequently, it has spread all over the world, and finally, on March 11, 2020, the World Health Organization (WHO) introduced this outbreak as a pandemic disease (2, 3).

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The virus uses angiotensin-converting enzyme 2(ACE2) for cellular attachment and penetration steps. In the early stages of the disease, studies supported the impression that children seemed to have a milder course and were less affected compared with adults (4). However, contrary to this belief, a new concern emerged with the introduction of an increasing number of cases similar to Kawasaki disease (KD) from England in April 2020 (5). Similar case reports from other European countries, Canada, and the United States soon followed. On May 14, the Centers for Disease Control and Prevention (CDC) named this emerging condition as a multisystemic inflammatory syndrome in children (MIS-C) (6). Although this new entity shared some similar features with KD, different clinical and laboratory findings started to be reported. For instance, myocardial and gastrointestinal (GI) involvement were more prominent in patients with MIS-C, and laboratory findings such as lymphopenia and thrombocytopenia were common, which were unexpected in KD.

In this study, we aimed to summarize the clinical and laboratory characteristics, treatments, and short-term outcomes of patients diagnosed with MIS-C.

Material and Methods

This cross-sectional study was performed between June 1, 2020 and December 1, 2020. Patients who were diagnosed with MIS-C were included in the study. Written informed consent was obtained from all participants, and the study protocol was approved by the Kocaeli University local ethics committee (2020/362). Patient data were recorded with a standard form, including demographic, clinical, and laboratory findings at the time of diagnosis and follow-up; treatments; and outcomes. All patients were initially asked whether they had contact with an individual with COVID-19. Subsequently, SARS-CoV-2 polymerase chain reaction (PCR) (Bio-speedy SARS CoV-2 Double Gene TR-qPCR Kit) and SARS-CoV-2 antibody (immunoglobulin [Ig] M and IgG) were tested. Complete blood count (CBC), biochemistry, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, procalcitonin, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, fibrinogen, troponin-I, pro-B-type brain natriuretic peptide (BNP), and viral serology tests were performed on admission. Furthermore, all patients have undergone chest radiography, electrocardiography (ECG), and echocardiography (ECHO).

The patients were diagnosed with MIS-C according to WHO (7) or CDC diagnostic criteria (6) (Supplementary Table I). All patients were tested for whether they fulfilled KD (8) and macrophage activation syndrome (MAS) classification criteria (9).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 21 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive analyses are presented as a percentage, median, and range. Categorical variables were compared with the chi-square test or Fisher's exact test where appropriate. Owing to the small number of patients, nonparametric tests were used. Mann-Whitney U test was used to compare variables between the two groups. The level of statistical significance was set at $P<0.05$.

Table 1. Clinical and laboratory findings of patients at the time of diagnosis

Demographic and clinical features	**Value**
Sex (M/F)	14/10
Age (month)	111 (10-180)
Duration of fever (days)	4 (2-12)
Duration of hospitalization (days)	8 (5-15)
Fever at admission	38.6 (37-41)
Complete blood cell counts	
White blood cell counts (cells/μL)*	7.680 (2.751-36.752)
Lymphocyte counts (cells/μL)*	866 (228-8.518)
Lymphopenia, n (%)	19 (79.1%)
Platelet counts (cells/μl)*	168.000 (56.400-1.050.000)
Thrombocytopenia, n (%)	11 (45.8%)
Inflammatory markers	
CRP (mg/dL)*	17.9 (1.4-34.4)
Elevated CRP, n (%)	24 (100%)
ESR (mm/hour)*	70 (9-140)
Elevated ESR, n (%)	22 (91.6%)
Ferritin (ng/mL)*	224 (35-1.353)
Elevated ferritin, n (%)	9 (37.5%)
Procalcitonin (ng/mL)*	1.7 (0.22-43)
Elevated procalcitonin, n (%)	24 (100%)
Coagulation tests	
D-dimer (μg/mL)*	2.1 (0.5-20)
Elevated D-dimer, n (%)	23 (95.8%)
INR	1.12 (0.85-1.54)
APTT (seconds)	27.6 (20-32.2)
Prothrombin time (seconds)	15 (11.4-20)
Fibrinogen (g/L)	4.9 (2.5-7.92)
Elevated fibrinogen, n (%)	19 (79.1%)
Cardiac markers	
NT-pro-BNP (pg/mL)*	1.650 (70-35.000)
Elevated NT-pro-BNP, n (%)	23 (95.8%)
Elevated troponin, n (%)	11 (45.8%)
Other biochemical tests	
Albumin (g/dL)*	3.4 (2.3-4.1)
Hypoalbuminemia, n (%)	12 (50%)
AST (U/L)*	30 (14-111)
Elevated AST, n (%)	8 (33.3%)
ALT (U/L)*	20 (8-112)
Elevated ALT, n (%)	7 (29.1%)
Sodium (mmol/L)	135 (128-140)
Hyponatremia, n (%)	10 (41.6)
Potassium (mmol/L)	4.1 (3.5-5.3)
Urea (mg/dL)*	23 (8.7-66)
Elevated urea, n (%)	3 (12.5%)
Creatinine (mg/dL)*	0.4 (0.2-1.9)
Elevated creatinine, n (%)	3 (12.5%)

*Data are expressed as median (minimum-maximum); ALT: alanine aminotransferase; APTT: activated prothrombin time; AST: aspartate aminotransferase; CRP: C-reactive protein; ERS: erythrocyte sedimentation rate; F: female; INR: international normalized ratio; M: male; NT-pro-BNP: N-terminal pro-b-type brain natriuretic peptide

Results

Study Population

A total of 24 patients were included in this study. Among them, 14 (58.3%) were male, and 10 (41.7%) were female. The median age was 111 (10-180) months. Among 24 patients, five aged <5 years, seven patients aged between 5 and 10 years, 9 patients aged between 10 and 15 years, and the remaining 3 patients aged >15 years (Figure 1).

One patient had methylmalonic acidemia, and one had cerebral palsy. The remaining 22 patients had no comorbidities. Two patients were overweight, and none were obese.

COVID-19 Test Results

A total of 17 patients (70.8%) revealed having contact with a patient with COVID-19. Among them, four patients had positive SARS-COV-2 PCR tests <1 month ago, whereas none had any symptoms at that time. The patients were diagnosed with MIS-C on a median of 30 (21-45) days after the contact. At the time of diagnosis, SARS-CoV-2 PCR was positive in three patients (12.5%). A total of 11 patients (45.8%) were positive for both SARS-CoV-2 IgG and IgM, whereas nine patients (37.5%) had positive IgG only. One patient was negative for both COVID-19 PCR and antibody, although he had a history of contact with an individual with symptomatic COVID-19 infection.

Clinical Findings

All patients met the CDC case definition criteria, whereas 23 patients fulfilled the WHO case definition. One patient was diagnosed with active COVID-19 infection initially and then developed MIS-C while in hospital. The median duration of hospitalization was 8 (5-15) days. All patients were brought to the emergency department with fever. The median duration of fever before admission was 4 (2-12) days. On admission, 12 patients (50%) had conjunctivitis, 11 patients (45.8%) had an erythematous rash, 10 patients (41.7%) had oral changes, three patients (12.5%) had extremity changes, and three patients (12.5%) had cervical lymphadenopathy. Three patients also had myalgia. Three patients (12.5%) met the classification criteria of KD, and six patients (25%) were diagnosed with incomplete KD (Figure 2).

Cardiovascular involvement was observed in 12 patients (50%). A total of 6 of the 12 patients with cardiac involvement had systolic dysfunction (ejection fraction [EF] <55%). Among them, five recovered in a short time, and one progressed to dilated cardiomyopathy with fulminant myocarditis. Coronary artery (CA) involvement was detected in four patients (16.6%), all of whom were mild. In the short-term follow-up, CAs were evaluated as normal in all of the patients. Pericardial effusion was present in four patients (16.6%), and mitral insufficiency was found in three patients (12.5%).

A total of patients (83.3%) had GI involvement. The most common GI symptom was abdominal pain (n=20), followed by nausea and vomiting (n=9) and diarrhea (n=2). Five patients (20.8%) presented with severe GI involvement. Of these, three had appendicitis, and two had pancreatitis. Three patients had tachypnea and decreased oxygen saturation; two patients had neurological involvement; one patient had a headache and neck stiffness and was diagnosed with meningitis; and one patient presented with headache and diplopia, with his cranial magnetic resonance imaging (MRI) revealing cytotoxic lesions in the corpus callosum. Four patients (16.6%) fulfilled the classification criteria of MAS.

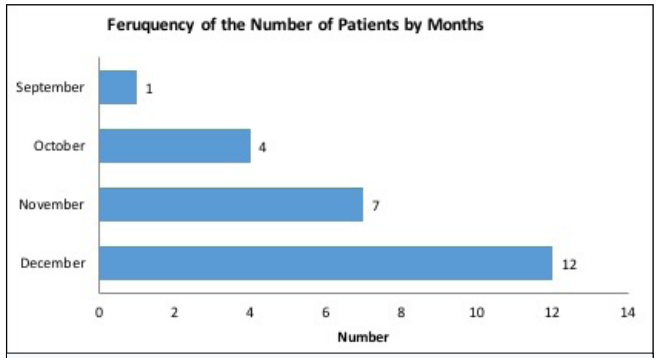

Figure 1. Frequency of the number of patients by months

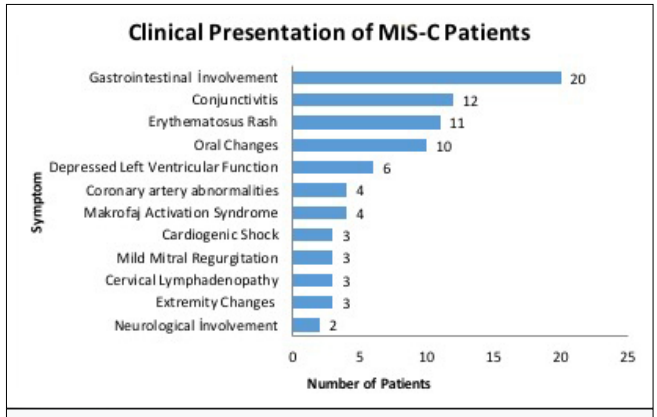

Figure 2. Clinical presentation of patients with MIS-C

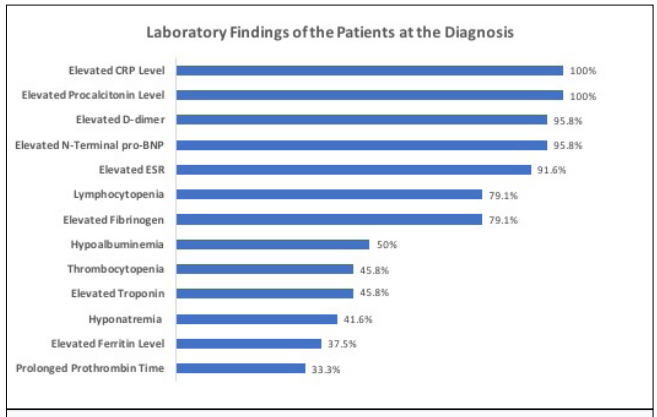

Figure 3. Laboratory parameters of patients with MIS-C

Laboratory and Radiological Investigations

The laboratory findings are presented in Table 1. In the initial laboratory evaluation, 19 patients (79.1%) had lymphopenia, and 11 patients (45.8%) had thrombocytopenia. All patients (100%) had increased levels of CRP and procalcitonin, whereas ESR was increased in 22 patients (91.6%), and ferritin was increased in 9 patients (37.5%). A total of 23 patients (95.8%) had an increased level of pro-BNP, and 11 patients (45.8%) had increased troponin-I levels (Table 1 and Figure 3). At the time of admission, blood and urine cultures were collected to

Table 2. Comparison of patients aged <5 years with those aged >5 years			
Variables	**Aged <5 years (n=5)**	**Aged >5 years (n=19)**	***P***
Sex (M/F)	2/3	12/7	0.615
Duration of fever (days)	4 (2-12)	4 (2-7)	0.731
Duration of hospitalization (days)	9 (7-11)	8 (5-15)	0.878
Fever at admission	38.5 (38-39)	38.6 (37.1-41)	0.629
Hemoglobin (g/dL)	10 (8.8-11)	11.6 (8.6-13.1)	0.19
White blood cell counts (cells/μL)*	17.542 (10.539-48.000)	7.800 (1.496-19.217)	0.007
Lymphocyte counts (cells/μL)*	4.075 (1.137-8.518)	809 (228-2.247)	0.001
Platelet counts (cells/μl)*	353.400(145.800-1.050.000)	125.000 (65.600-547.900)	0.075
C-reactive protein (mg/dL)*	156 (14-221)	200.8 (20.7-310)	0.183
Erythrocyte sedimentation rate (mm/hour)*	62 (47-84)	67 (9-112)	0.235
Ferritin (ng/mL)*	115 (44-144)	294 (35-1,353)	0.015
Procalcitonin (ng/mL)*	0.64 (0.22-1.3)	2.2 (0.3-24)	0.257
D-dimer (μg/mL)*	4.2 (0.6-20)	2.5 (0.5-12.1)	0.629
International normalized ratio	1.22 (1.03-1.37)	1.08 (0.85-1.3)	0.103
Activated prothrombin time (seconds)	27.3 (20-32)	27.7 (22-31)	0.731
Prothrombin time (seconds)	16.2 (14.7-17.5)	14.8 (11.4-17.8)	0.063
Fibrinogen (g/L)	4.6 (2.5-5.64)	5 (2.5-7.9)	0.208
NT-pro-BNP (pg/mL)*	684 (343-1540)	2.300 (70-35,000)	0.406
Troponin I ng/L	0-76	0-200	0.406
Albumin (g/dL)*	38 (28-41)	33 (23-40)	0.235
Aspartate aminotransferase (U/L)*	27.25 (14-49)	31.9 (24-111)	0.836
Alanine aminotransferase (U/L)*	32 (8-58)	26 (12-112)	0.945
Sodium (mmol/L)	136.3 (132-139)	135 (132-136)	0.075
Potassium (mmol/L)	4.5 (4-4.8)	4 (3.5-5.3)	0.103
Creatinine (mg/dL)*	0.28 (0.24-0.40)	0.4 (0.2-0.75)	0.024
F: female; M: male; NT-pro-BNP: N-terminal pro-b-type brain natriuretic peptide.			

rule out sepsis. All cultures were negative. None of the patients had arrhythmia on ECG. ECHO revealed pericarditis without significant pericardial effusion in four patients (16.6%), CA dilatation in three patients (12.5%), CA brightness in one patient (4.1%), marked regional motion defect in two patients (8.3%), and mild mitral regurgitation in three patients (12.5%). The median levels of EF and the shortening fraction (SF) were 65 (30-74) and 35 (14-42), respectively. EF was <55% in six patients (50%), and SF was <28% in five patients. Cardiac MRI showed intramyocardial contrast involvement of the left ventricle lateral wall in three patients who were diagnosed with myocarditis.

Chest radiography was performed for all the patients and was found to be normal except for three patients. Bilateral interstitial infiltrates together with ground grass opacities in thorax computerized tomography were detected in these three patients. Moreover, SARS-CoV-2 PCR tests were negative in them. All the patients with GI involvement underwent abdominal ultrasonography. Among them, ultrasonography revealed appendicitis in three and pancreatitis in two patients. Appendectomy was performed on two patients.

Comparison of Patients According to Age

The differences between children aged <5 years and those aged >5 years are summarized in Table 2. There were no significant differences in terms of clinical and laboratory findings except in white blood cell count, lymphocyte counts, ferritin levels, and creatinine levels. White blood cell count and lymphocyte count were significantly higher in patients aged <5 years. However, the differences may be explained by the variability of these parameters by age.

Characteristics of the Patients with Severe Manifestations

A total of 11 patients were classified as severe on the basis of myocarditis being present, neurologic involvement, severe GI findings. When data were compared with those of patients without severe manifestations, there was no statistical significance in terms of demographic, clinical, and laboratory findings except for the level of procalcitonin. The median levels of initial procalcitonin level were higher in patients with severe phenotype than in others (2.35 vs 0.78, p=0.03). The median pro-BNP level was higher in patients with severe phenotype but did not reach statistical significance. Furthermore, the levels of D-dimer returned to normal more slowly in patients classified as severe (10 days vs 7 days, *p*=0.02) (Table 3).

Treatments and Short-term Outcomes

All the patients received intravenous Ig (IVIG) (2 g/kg), and one patient required a second dose of IVIG. Methylprednisolone (2 mg/kg/day) was administered to 10 patients. Four patients were initially treated with pulse methylprednisolone for 3 consecutive days (15-30 mg/kg/day; maximum dose: 1,000 mg/day) and then continued with a 2 mg/kg/day dosage. The patients who were treated with pulse methylprednisolone had severe manifestations. Steroid treatment was tapered within 3 weeks. Prophylactic low-molecular-weight heparin (1 mg/kg/day) was initiated for all the patients, and all of them were discharged with an antiaggregant dose of acetylsalicylic acid (3-5 mg/kg/day). Hypotension requiring inotropic support was

Table 3. Comparison of patients with severe phenotype with those without severe phenotype

Variables	Mild-moderate phenotype	Severe phenotype	*P*
Sex (M/F)	5/7	9/3	0.098
Age (month)	114 (10-180)	126 (10-208)	0.630
Duration of fever (days)	4 (3-12)	3.5 (2-7)	0.219
Fever at admission	38.4 (37-41)	38.7 (38-39.9)	0.219
Duration of hospitalization (day)	8 (5-12)	9 (7-15)	0.179
Hemoglobin (g/dL)	10.8 (9.9-13.1)	10.9 (8.6-12.5)	0.551
White blood cell counts (cells/µl)*	10.049 (4.819-48.000)	8.969 (1.496-19.217)	0.266
Lymphocyte counts (cells/µl)*	882 (228-8518)	842 (285-2247)	0.551
Platelet counts (cells/µl)*	168.000 (72.900-1.050.000)	182.000 (56.400-547.900)	0.887
C-reactive protein (mg/dL)*	173.5 (14.4-306.2)	183.5 (20.7-344)	0.887
Erythrocyte sedimentation rate (mm/hour)*	67 (35-112)	75.5 (9-140)	0.755
Ferritin (ng/mL)*	135.3 (35-1341)	379 (44-1353)	0.198
Procalcitonin (ng/mL)*	0.78 (0.22-23)	2.35 (1-43)	0.032
D-dimer (µg/mL)*	1.87 (0.5-20)	2.09 (1.2-12)	0.843
INR	1.13 (1.03-1.37)	1.11(0.96-1.54)	0.887
Activated prothrombin time (seconds)	27.4 (20-32)	27.7 (22-30)	0.843
Prothrombin time (seconds)	15 (11.7-17.8)	15 (13.1-20)	0.671
Fibrinogen (g/L)	5 (2.87-7.19)	4.55 (2.53-7.92)	0.410
NT-pro-BNP (pg/mL)*	1.244 (70-16.000)	3.440 (266-35.000)	0.291
Troponin I ng/L	0-200	0-76	0.551
Albumin (g/dL)*	34.7 (28-40)	35 (23-41)	0.977
Aspartate aminotransferase (U/L)*	29.5 (14-61)	32.4 (21-111)	0.443
Alanine aminotransferase (U/L)*	30 (8-58)	18.5 (9-112)	0.378
Sodium (mmol/L)	135.3 (128-139)	134.9 (131-140)	1.000
Potassium (mmol/L)	4.26 (3.6-4.8)	3.9 (3.5-5.3)	0.242
Creatinine (mg/dL)*	0.41 (0.24-0.75)	0.36 (0.2-5)	0.713

F: female; INR: international normalized ratio; M: male; NT-pro-BNP: N-terminal pro-b-type brain natriuretic peptide.

observed in three patients (12.5%). Anti-interleukin-1 (anakinra) was given to two patients. These two patients were unresponsive to IVIG and pulse methylprednisolone. Among them, one had fulminant myocarditis, and one had a fever that was resistant to IVIG and steroid therapy. After anakinra initiation, fever resolved in this patient, but the patient with fulminant myocarditis developed dilated cardiomyopathy, was listed for cardiac transplantation, and died on day 74. Clinical findings resolved in the other patient receiving anakinra on day 2. Anakinra administration was stopped on day 7 after initiation. Two patients were admitted to the intensive care unit (ICU). Of these two patients, one had fulminant myocarditis as mentioned earlier, and one had hypotension requiring inotrope therapy and recovered 2 days after IVIG and steroid therapy and was transferred to the ward. The median time of hospitalization was 8 (5-15) days. The length of hospitalization and the time to normalization of laboratory findings were not different between patients receiving steroids and patients treated without steroids ($P>0.05$).

The lymphocyte counts and pro-BNP, CRP, and D-dimer values of the patients became normal on the median day of 6 (4-9), 7 (6-8), 10 (9-12), and 9 (6-12) days, respectively. A total of 23 patients were discharged without morbidity, and all were evaluated on the median day of 68.5 (52-140) days after discharge. There was no mortality within this period in these 23 patients. Control echocardiograms were normal in 22 patients. One of the patients who had initially presented with left ventricular systolic dysfunction had slightly low EF (55%) at short-term follow-up after discharge. Patients were discharged on an antiaggregant dose of acetylsalicylic acid (3-5 mg/kg/day), and they continued on it for 2 months. The remaining one patient with dilated cardiomyopathy died after 2 months in the ICU owing to cardiac failure.

Discussion

Since the introduction of MIS-C, presentations with a wide range of clinical findings have been reported. In this study, 24 patients with MIS-C were evaluated, and their short-term outcomes were presented. Although COVID-19 has a milder course in most children, severe MIS-C cases have been reported even after asymptomatic infections. Among our 24 patients, four had asymptomatic infection 1 month before the diagnosis of MIS-C.

Previous studies showed that patients with MIS-C had a fever and mucocutaneous features similar to those with KD, which is the second most common vasculitis of childhood. Therefore, in the beginning, this new entity was announced as Kawasaki-like syndrome (10). However, it is now well known that patients with MIS-C exhibit some major differences. For instance, MIS-C was observed in older patients, and unlike KD, it was more common in Afro-American ethnicity. Recently, data on MIS-C from different populations have been reported. These studies supported that it is an important problem in all populations regardless of ethnicity. According to three large series, 25-45% of patients belonged to the Afro-American ethnicity, 30-40% were Hispanic, 15-25% were Caucasian, and 3-28% were Asian (11-13). In these aforementioned studies, the median age was 8-11

years, whereas classical KD is more common in children aged <5 years and those from Asia. To reveal the reason for the occurrence of MIS-C in older children, many hypotheses were introduced. Researchers have suggested that frequent contacts with other coronaviruses in the first years of life may cause cross-immunity or that the immune system of young children may respond more aggressively owing to early childhood vaccinations. Furthermore, studies showed that the expression of ACE2 receptors was lower in young children (14). Correspondingly, in this study, the median age at diagnosis was older.

Apart from the epidemiologic differences, patients with MIS-C exhibit some different findings from patients with KD. Cardiovascular involvement is predominant both in KD and MIS-C, whereas the nature of this involvement is different between the two. Myocardial involvement is prominent in patients MIS-C, whereas patients with KD present with a CA involvement more frequently. It is thought that the main mechanism of organ damage in patients with MIS-C is due to antigen-antibody-mediated cytokine storm (15). The underlying factors of myocardial injury in MIS-C are still unclear. Some researchers suggest that systemic inflammation, acute viral myocarditis, hypoxia, stress cardiomyopathy, and rarely, ischemia caused by CA involvement may be the possible causes (16). Matsubara et al. (17) showed that systolic and diastolic functions were worse in children with MIS-C than in those with classic KD, whereas CA involvement was less common in patients with MIS-C.

Myocardial dysfunction by ECHO and/or increased troponin-I or pro-BNP levels were reported in 51-90% of patients with MIS-C (11, 13, 16, 18, 19). In our cohort, 5 patients (20.8%) had myocarditis, and pro-BNP and troponin-I levels were elevated in 23 patients (95.8%) and eight patients (33.3%), respectively. EF was <55% in six patients (50%), and SF was <28% in five patients. Cardiac involvement may be detected more easily using strain and tissue Doppler than using conventional ECHO. Theocharis et al (20) showed strain and tissue Doppler indices to be abnormal in almost all patients with MIS-C at the time of admission. CA abnormalities may be observed in 8-19% of patients with MIS-C (11, 19). The rate of CA dilatation was 12.5% in our study.

Previous studies also showed that 22-64% of patients with MIS-C fulfilled the classification criteria for KD (11, 13,16, 18, 19). Of our 24 patients, three (12.5%) fulfilled the classification criteria of KD, whereas findings in six patients (25%) were compatible with incomplete KD. The GI tract is rarely affected in patients with KD, whereas GI involvement was observed in most of the patients with MIS-C. The most common GI features were abdominal pain, vomiting, and diarrhea (12, 21, 22). Previous data on severe GI involvement were confined to case reports (17-19). In this study, 83.3% of patients had GI involvement. Among them, five patients had severe GI manifestations presenting as appendicitis in three and pancreatitis in two patients. Studies have shown that ACE2 receptors are abundant in the myocardium and GI tract (23). These findings supported the high prevalence of GI and myocardial involvement in patients with MIS-C.

Lymphopenia was observed in up to 80% of patients with MIS-C. Thrombocytopenia was found in 31-80% of the patients. Elevated inflammatory markers, such as ESR, CRP, ferritin, D-dimer, and procalcitonin, were also reported (11, 13, 16, 18, 19). Elevated inflammatory markers seemed to be associated with a severe course. Whittaker et al. (21) reported that children with shock had higher CRP and neutrophil counts and lower lymphocyte counts than children without shock. In our study, we showed that patients with severe disease had higher levels of procalcitonin.

The neurotropic and neuroinvasive potentials of coronaviruses have been reported previously. Coronaviruses can enter the central nervous system (CNS) through the olfactory bulb during nasal infection and result in CNS inflammation and demyelination. However, the main underlying factors related to neurological involvement in children with MIS-C have not been elucidated yet. The absence of virus in the cerebrospinal fluid and generally the lack of lung involvement in these patients supported the existence of other factors. Researchers suggest that cellular edema of neurons due to inflammatory response and immune-mediated neuronal damage may be the reason for the neurological manifestation in children with MIS-C (24). According to studies, patients having severe neurological complications accounted for about 5% of patients with MIS-C (11). In our study, we report two children (8%) manifesting severe neurological complications, one of whom had meningitis and bilateral thalamic lesions, and the other had a cytotoxic lesion of the corpus callosum.

American College of Rheumatology (ACR) has announced the launch of a clinical guideline for the management of patients with MIS-C (25). According to this guideline, IVIG and/or glucocorticoids are recommended as a first-line treatment, although there are no evidence-based data on the management of patients with MIS-C. Jonat et al. (26) showed that early initiation of IVIG and glucocorticoids in MIS-C reduced ICU admissions and length of hospital stay. Belhadjer et al. (27) reported faster recovery with IVIG and methylprednisolone in patients with MIS-C with myocarditis than with IVIG monotherapy. Accordingly, the ACR guideline contains a recommendation that glucocorticoids may be added to IVIG as first-line therapy in patients with an ill appearance, highly elevated pro-BNP, or unexplained tachycardia. We were unable to demonstrate any differences between patients receiving steroids and those treated without steroids.

Currently, there are insufficient data about long-term outcomes of patients with MIS-C, but studies about short-term outcomes are emerging. Ramcharan et al. (5) reported no deterioration in cardiac function of their 12 patients with MIS-C at the first-week control ECHO after discharge. Clouser et al (28) presented favorable short-term outcomes with a multidisciplinary approach in 20 patients with MIS-C. They reported that among 13 patients with cardiac involvement, 11 had follow-up ECHO within 30 days after discharge. Of these 11 patients, nine had normal echocardiograms, one had CA dilatation, and one had declining left ventricular function. In comparison, we managed to discharge 23 of our patients with full recovery, and their control echocardiograms were normal in the first month of follow-up.

Our study is limited by its single-center design and small sample size. Furthermore, inadequate data on long-term outcomes of patients are another restriction.

Conclusion

Although children show milder symptomatology of COVID-19, MIS-C emerges as a serious consequence of this outbreak. Patients with MIS-C are older than those with classic KD, and most of them present with GI and cardiac involvement. We would like to underline the importance of a multidisciplinary approach that we think has been successfully implemented in our institution for early diagnosis and appropriate treatment.

Ethical Committee Approval: Ethical committee approval was received from the Kocaeli University local ethics committee (2020/362).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Supplementary Table 1. WHO and CDC case definitions of multisystem inflammatory syndrome in children	
CDC case definition	
All 4 criteria must be met	
1.	Age <21 years
2.	Clinical presentation consistent with MIS-C, including all of the following:

	• Fever
	• Documented fever >38.0°C (100.4°F) for ≥24 hours
	• or
	• Report of subjective fever lasting ≥24 hours
	• Laboratory evidence of inflammation, including but not limited to any of the following:
	  • Elevated CRP
	  • Elevated ESR
	  • Elevated fibrinogen
	  • Elevated procalcitonin
	  • Elevated D-dimer
	  • Elevated ferritin
	  • Elevated LDH
	  • Elevated IL-6 level
	  • Neutrophilia
	  • Lymphocytopenia
	  • Hypoalbuminemia
	• Multisystem involvement
	• 2 or more organ systems involved:
	  • Cardiovascular (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)
	  • Respiratory (e.g., pneumonia, ARDS, pulmonary embolism)
	  • Renal (e.g., AKI, renal failure)
	  • Neurologic (e.g., seizure, stroke, aseptic meningitis)
	  • Hematologic (e.g., coagulopathy)
	  • Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding)
	  • Dermatologic (e.g., erythroderma, mucositis, other rashes)
	• Severe illness requiring hospitalization

3.	No alternative plausible diagnoses
4.	Recent or current SARS-CoV-2 infection or exposure
	Any of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • COVID-19 exposure within the 4 weeks before the onset of symptoms
WHO case definition	
All 6 criteria must be met.	
1.	Aged 0-19 years
2.	Fever for ≥3 days
3.	Clinical signs of multisystem involvement (at least 2 of the following):
	• Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) • Evidence of coagulopathy (prolonged PT or PTT or elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4.	Elevated markers of inflammation (e.g., ESR, CRP, or procalcitonin)
5.	No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6.	Evidence of SARS-CoV-2 infection
	• Any of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; BNP: brain natriuretic peptide; CDC: Center for Disease Control and Prevention; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; LDH: lactic acid dehydrogenase; MIS-C: multisystem inflammatory syndrome in children; PT: prothrombin time; PTT: partial thromboplastin time; RT-PCR: reverse transcriptase-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization.